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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/866,034	05/25/2001	David Botstein	P2930R1C1	4767

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EXAMINER
SPECTOR, LORRAINE

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/14/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

[redacted]

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 1/11/02

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 22-34 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 22-34 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 3
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

Part III: Detailed Office Action

Claims 22-34 are pending and under consideration.

Formal Matters:

The deposit of biological organisms is considered by the Examiner to be necessary for enablement of the current invention (see MPEP Chapter 2400 and 37 C.F.R.§§1.801-1.809). Examiner acknowledges the deposit of organisms under accession number ATCC 203538 under terms of the Budapest Treaty on International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure in compliance with this requirement (see specification, page 130).

Objections and Rejections under 35 U.S.C. §112:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 22-34 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility.

The claims are directed to isolated polypeptides having at least 80% identity to a SEQ ID NO: 2 with or without its signal peptide, or to the extracellular domain of SEQ ID NO: 2 with or without its signal peptide. Dependent claims are directed to vectors and host cells comprising the isolated nucleic acids. Finally, claims are presented to chimeric proteins comprising the aforementioned polypeptides. The specification contains numerous asserted utilities at pages 81-98 including use as hybridization probes, in chromosome and gene mapping, in the generation of anti-sense RNA and DNA, to identify molecules that bind to PRO (including agonists and antagonists), to make "knock-out" mice or other animals, in gene therapy, as molecular weight markers, therapeutic agents, and for the production of antibodies. The utilities that pertain solely to nucleic acids (e.g. hybridization, chromosome and gene mapping, anti-sense) would not convey to the encoded protein. With respect

to the remaining utilities, none of these asserted utilities is specific for the disclosed PRO1800 protein, as each of the aforementioned utilities could be asserted for any naturally occurring protein, and further, as none of the asserted utilities requires any feature or activity that is specific to the disclosed PRO1800.

The specification teaches that PRO1800 has (unspecified) homology to Hep27, which Hep27 is a member of the short chain alcohol dehydrogenase protein family (page 2). At page 70, the specification states that PRO1800 is a "newly identified Hep27 homolog, and possesses activity typical of that protein", however no activity is known or disclosed for Hep27. The structure of the putative PRO1800 peptide is discussed at page 103 of the specification, however there is no disclosure that the protein is expected to be a transmembrane protein, nor of any extracellular domain. There is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with PRO1800. Without any information as to the specific properties of PRO1800, the mere identification of such as belonging to the "short chain alcohol dehydrogenase protein family" is not sufficient to impart any particular utility to the claimed polypeptides.

At pages 116-117, it is disclosed that nucleic acids encoding PRO1800 had a ΔCt value of at least 1.0 for a number of primary lung and colon tumors, but not for all but one of the tested colon or lung tumor cell lines. At page 113, ΔCt is defined as the threshold PCR cycle, or the cycle at which the reporter signal accumulates above the background level of fluorescence. The specification further indicates that ΔCt is used as "a quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results." The Examiner is unable to find, either in the specification or in the art, an explanation of how ΔCt values are calculated, nor what the significance of such are. It is noted that at the penultimate paragraph of page 116, it is stated that samples are used if their values are within 1 Ct of the 'normal standard'. It is further noted that the ΔCt values at page 117 are expressed (a) with values to one one-hundredth of a unit (e.g. 2.58), and (b) that only one sample, "LT19", gave values that were consistently (at least on a sample size of 2) at least 2. It is not clear

how measurements of hundredths of a PCR cycle can be made, nor what the significance of a difference of 1 or 2 PCR cycles would be. Given the paucity of information, the data do not support the implicit conclusion of the specification that PRO1800 shows a positive correlation with lung and colon cancer, much less that the levels of PRO1800 would be diagnostic of such. Even *if* the data demonstrated a slight increase in copy number of PRO1800 nucleic acids in primary tumors, such would not be indicative of a use of the encoded polypeptide as a diagnostic agent. Cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes (see Sen, 2000, Curr. Opin. Oncol. 12:82-88). The data presented in the specification were not corrected for aneuploidy. A slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. The preliminary data were not supported by analysis of mRNA or protein expression, for example. Thus, the data do not support the implicit assertion that PRO1800 can be used as a cancer diagnostic. Significant further research would have been required of the skilled artisan to determine whether PRO1800 is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic, and thus the implicitly asserted utility is not substantial.

Not addressed

It is noted that even if utility is eventually established for PRO1800, issues of claim scope under 35 U.S.C. § 112, first paragraph would remain regarding lack of teachings or guidance as to which molecules having 80% homology would be useful for any particular disclosed use.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-34 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 22-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity with a particular disclosed sequence. The claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity. Further, the claims require the 'extracellular domain' of the protein, for which there is no description in the specification.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction

to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 2, with or without the signal sequence, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The protein identified as PRO1800 is not disclosed as being expressed on a cell surface. Accordingly, the limitation that the claimed protein comprises an "extracellular domain" (for example see claim 22 parts (c) and (d)) is indefinite, as the art does not recognize soluble proteins as having such domains. Further, if the protein had an extracellular domain, the recitation of "the extracellular domain"..."lacking its associated signal sequence" (claim 22, part (d), for example) is indefinite as a signal sequence is not generally considered to be part of an extracellular domain, as signal sequences are cleaved from said domains in the process of secretion from the cell.

Priority Determination:

As the claimed subject matter is found to lack utility and enablement under 35 U.S.C. § §101 and 112, first paragraph, respectively, the effective priority date for this application is the instant filing date, 5/25/01.

Rejections over Prior Art:

A search of the protein sequence databases revealed the following prior art:

Locus	Date	Author	Identity to SEQ ID NO:2
Q9BTZ2	2/01	Strausberg	100%
Q9H3N5	6/00	Furukawa	100%, residues 19-278
O95162	5/1/99	Fransen	99.2%, residues 19-278
AF044127	5/27/99	Fransen	99.3% (1 conservative sub.)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 22-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Fransen et al. locus O95162. As summarized above, Fransen et al. disclose locus O95162, which has 99.2% identity to SEQ ID NO: 2 lacking its signal peptide, i.e. residues 19-278 of SEQ ID NO: 2.

Claims 22-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Fransen et al. locus

[redacted]

AF044127. As summarized above, Fransen et al. disclose locus AF044127, which has 99.3% identity to the entirety of SEQ ID NO: 2 .

Claims 22-29 and 32 are rejected under 35 U.S.C. 102(a) as being anticipated by Strausberg, locus Z9BTZ2, or Furukawa et al., locus Q9H3N5. As summarized above, the two proteins are 100% identical to the entirety of SEQ ID NO:2, and 100% of residues 19-278 of SEQ ID NO: 2, which is the polypeptide lacking its signal sequence.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27-29 and 32 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Fransen et al. locus O95162 or locus AF044127.

As discussed above, Fransen et al. disclose an isolated two polypeptides having over 99% amino acid sequence identity to the amino acid sequence of the polypeptide shown in SEQ ID NO: 2. The single difference in amino acid sequence between the polypeptide of SEQ ID NO: 2 recited in the instant claims and the polypeptides of Fransen et al. occurs at position 126. Specifically, the

amino acid at position 126 in SEQ ID NO: 2 of the instant application is isoleucine, whereas the corresponding amino acid of Fransen et al. is leucine. This is a conservative amino acid substitution.

The courts have long recognized that sequencing errors can occur (*Ex parte Maizel*; 27 USPQ2d 1662, BPAI 1992, see especially pp. 1663 and 1666). The instant specification also recognizes that the sequences disclosed in their sequence listings and Figures may not be exact. At page 70 of the instant specification, it is stated that:

> "For the PRO polypeptides and encoding nucleic acids described herein, Applicants have identified what is believed to be the reading frame best identifiable **with the sequence information available at the time.**" (emphasis added)

Therefore, it is reasonable to expect that the single amino acid difference at position 126 of SEQ ID NO: 2 of the instant application and Fransen et al. may be the result of a sequencing error, and that the actual clones of the instant application and Fransen et al., in fact, have identical sequences.

The examiner is unable to determine whether the prior art disclosures actually possesses the characteristic of the sequence of SEQ ID NO: 2. Under such circumstances, where the product seems to be identical, then the burden shifts to applicant to provide evidence that the prior art would neither anticipate nor render obvious the claimed invention. Note the case law of *In re Best* 195 USPQ 430, 433 (CCPA 1977).

Claims 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Fransen et al. locus O95162 or locus AF044127, or Strausberg, locus Z9BTZ2, or Furukawa et al., locus Q9H3N5, any one in view of Hopp et al., U.S. Patent Number 5,011,912.

The teachings of the four primary references are cited above. All of the protein sequences are clearly identified as being from nucleic acid sequence, indicating that the nucleic acids encoding the protiens had been cloned. None of the primary references teaches expression of the protein as a fusion protein comprising an epitope tag or Fc region.

Hopp et al. teach the use of an amino acid sequence, "DYKDDDDK", which is disclosed as

being immunogenic, for use in producing fusion protiens which can then be easily purified. See, for example, column 2, lines 45-57. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the protein of any one of the primary references by producing such as a fusion protein comprising the flag amino acid sequence of Hopp et al., for the purpose of being able to easily purify the proteins of the primary references. The motivation and expectation of success are both taught by Hopp et al. who teach the flag peptide/monoclonal antibody purification system as being generally useful for such.

Advisory Information:

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 5:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary L. Kunz, at (703)308-4623.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to (703) 746-5228.

Lorraine Spector, Ph.D.
Primary Examiner

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